Fibrinogen Synthesis. The paragraph is written as though (2) Pilgeram and Pickart associated their Results with cigarette smoking. The association was added by somebody else. There is no mention of cigarette smoking in Pilgeram and Pickart's article. Note that the transposition of results is increasing by one step as follows: cigarette smoking ⟶ release of epinephrine ⟶ elevation of FFA ⟶ fibrinogen synthesis ⟶ clotting ⟶ atherosclerosis.

DISCUSSION

A role for FFA in the turnover of fibrinogen could have been predicted by the correlation of a number of earlier studies. For example, incorporation of glycine into fibrinogen is enhanced by epinephrine[5,9]. However, epinephrine is well known to mobilize FFA[10]. ACTH has been reported to raise the plasma content of fibrinogen[11,12]. ACTH administration has been shown to induce elevation in plasma FFA and to induce thrombosis[13]. Chronic stress syndromes have been associated with elevations in plasma fibrinogen[14-16]. However stress has also been found to induce an output or increase of epinephrine, cholesterol, and FFA[17-20]. Stress has also been associated with myocardial infarction or coronary thrombosis[21]. Cortisone, depending upon dosage, induces an increase in fibrinogen[22] or a decrease[23]. Cortisone also restores the mobilization of FFA in adrenalectomized animals exposed to trauma[10], etc.

Correlation of a number of reports also suggests a role for FFA in the formation of fibrin or fibrinogen-fibrin intermediates. Saturated long chain fatty acids shorten the clotting time and accelerate thrombus formation[24-27], activate Hageman factor[28], aggregate platelets[29], activate plasma thromboplastin antecedent[30], and induce thrombosis *in vivo*[27]. Although the clot promoting effect of FFA has been confirmed by a number of investigators, a failure of the fatty acid salt to accelerate the clotting of native plasma *in vitro*, *i.e.*, plasma that had not been decalcified, has been reported[30]. On the basis of this study, the authors concluded that it seemed doubtful that FFA are of importance in the development of intravascular thrombi. However, this con-

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clusion requires reexamination in view of the study which showed that thrombi were induced *in vivo* by the infusion of fatty acid salts[27]. In these latter experiments the fatty acid salt entered into native plasma and still induced thrombi. From these considerations and from the data reported in this paper, it would appear warranted to suggest that FFA not only control the rate of synthesis or turnover of the soluble precursor of the clot forming protein, fibrin, but also play a significant role in determining the rate of formation of fibrin or precursors thereof. The enhanced rate of turnover of fibrinogen[4] is indicative of both an increase in the rate of biosynthesis and an increase in utilization. Study of the turnover rate does not in itself show the nature of the enhanced pathways of utilization. It is therefore pertinent to consider those reports which bear upon the nature of the pathway(s) of utilization of fibrinogen which are enhanced by FFA. The correlation of an enhanced turnover rate of fibrinogen with coronary thrombosis[4] and with changes in blood clotting indices, which are indicative of enhanced generation of thrombin, is suggestive of an increase in the formation of fibrin or fibrinogen-fibrin intermediates. For example, enhanced generation of plasma thromboplastin[31,32] and a deficiency in plasma antithromboplastin[33] are found in thrombotic complications. An enhanced level of antithrombin[34], possibly a protective feed-back mechanism against thrombin, is found in coronary thrombosis. An increased concentration of plasma fibrinogen is also found in coronary thrombosis[1,4,31]. This increase has been shown to correlate with the enhanced rate of biosynthesis and utilization[4]. Our recent study, which shows that thrombin induces, *in vivo*, a significant increase, up to 1.9-fold, in the rate of biosynthesis of fibrinogen[35] suggests that the enhanced rate of turnover reflects conversion of fibrinogen to fibrin. These correlations are made with an awareness that the platelets play an important role in the formation of thrombi. However, it has been recently shown that platelets will not clump unless fibrinogen is present[36]. The role of fibrinogen, fibrin, and thrombin in the clumping and utilization of platelets was recently reviewed[37]. The fact that thrombin not only enhances the turnover of platelets but also the turnover of fibrinogen[4] combined with the observations that both the turnover of platelets[38] and the turnover of fibrinogen[4] are enhanced in coronary artery disease suggests that conversion to fibrin is a significant pathway in the enhanced turnover of fibrinogen.

A control by FFA over the metabolism of fibrinogen may have implications with respect to unifying the two theories on atherogenesis which are based either on disturbed fat metabolism or on blood clotting. The intravascular deposition of fibrin-platelet thrombi has been implicated as a cause of arteriosclerosis since the time of Vos Rokitansky[39]. Numerous recent histological investigations show that thrombi on the vessel surfaces give rise to intimal thickening and eventually arteriosclerosis[40-47]. Recently, injections of thrombin into the areas of the intima and the media were shown to produce atheroma[48].

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